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1.	Your reference	PCB/P089202PGB 0221248.8
2.	Patent application number *(The Patent Office will fill in this part)*	13 SEP 2002
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	THE VICTORIA UNIVERSITY OF MANCHESTER OXFORD ROAD MANCHESTER M13 9PL
	Patents ADP number *(if you know it)*	07391550 01
	If the applicant is a corporate body, give the country/state of its incorporation	UNITED KINGDOM
4.	Title of the invention	TREATMENT OF BASAL GANGLIA-RELATED MOVEMENT DISORDERS
5.	Name of your agent *(if you have one)*	Marks & Clerk
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	43 Park Place Leeds LS1 2RY
	Patents ADP number *(if you know it)*	18013

6.	If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing *(day/month/year)*
7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing *(day/month/year)*
8.	Is a statement of Inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:* *a) any applicant named in part 3 is not an inventor, or* *b) there is an inventor who is not named as an applicant, or* *c) any named applicant is a corporate body.* *See note (d))*	YES		

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Description	16
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Priority documents	-
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Statement of Inventorship and right to grant of a patent *(Patents Form 7/77)*	-
Request for preliminary examination and search *(Patents Form 9/77)*	1/
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11. I/We request the grant of a patent on the basis of this application.

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TREATMENT OF BASAL GANGLIA-RELATED MOVEMENT DISORDERS

The present invention relates to the treatment of basal ganglia-related movement disorders and particularly dyskinesias.

Dyskinesias are abnormal involuntary movement disorders. The abnormal movements may manifest as chorea or ballism (irregular, involuntary movements of the body, face and extremities) or dystonia (disorder of muscle tone and body posture).

Movement and other disorders due to dysfunction of the basal ganglia and related brain structures are of major socio-economic importance. Such disorders can occur as a consequence of inherited or acquired disease, idiopathic neurodegeneration or they may be iatrogenic. The spectrum of disorders is very diverse, ranging from those associated with poverty of movement (akinesia, hypokinesia, bradykinesia) and hypertonia (e.g. Parkinson's disease, some forms of dystonia) to the involuntary movement disorders (hyperkinesias or dyskinesias e.g. Huntington's disease, levodopa-induced dyskinesia, ballism, some forms of dystonia).

Knowledge of the pathophysiological mechanisms that underlie some of these disorders makes it likely that similar mechanisms mediate disorders characterised by either hyperkinesias or dyskinesias. It is to be expected, therefore, that treatments that are effective in one form of dyskinesia may be beneficial in dyskinesias of different aetiology.

One common way in which dyskinesias arise is as a side-effect of dopamine replacement therapy for parkinsonism or other basal ganglia-related movement disorders. Parkinsonism is a syndrome of symptoms characterised by slowness of movement (bradykinesia), rigidity and/or tremor. Parkinsonian symptoms are seen in a variety of conditions, most commonly in idiopathic parkinsonism (i.e. Parkinson's disease) but also following treatment of schizophrenia, exposure to toxins/drugs and head injury. In Parkinson's disease the primary pathology is degeneration of dopaminergic neurons of the substantia nigra, pars compacta.

The most widely used symptomatic treatments for parkinsonism use dopamine-replacing agents (e.g. L-DOPA and dopamine receptor agonists). These do, however, have limitations, especially following long-term treatment. Problems can include a "wearing-off" of the anti-parkinsonian efficacy of the treatment and in particular the appearance of a range of side-effects. These side-effects may manifest as dyskinesias such as chorea and dystonia. Dyskinesia can be seen either when the patient is undergoing dopamine-replacement therapy (in the case of chorea and/or dystonia) or even when off therapy (when dystonia is prevalent). Ultimately, these side-effects severely limit the usefulness of dopaminergic treatments.

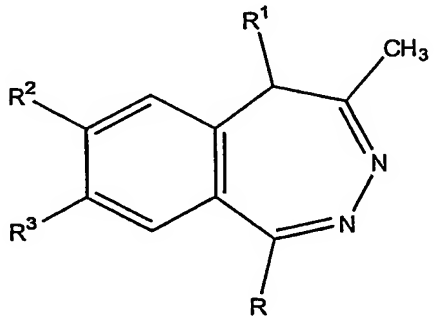
Another common cause of dyskinesias is the treatment of psychosis with neuroleptic drugs – this is known as tardive dyskinesia.

Dyskinesia also occurs in many other conditions including:

- Huntington's disease
- idiopathic dystonia
- Tourette syndrome
- "off" dystonia in parkinsonism
- ballism
- senile chorea

Many attempts have been made to develop agents that will prevent the development of, and/or treat, dyskinesias although such attempts have met with limited success. There is, therefore, a need to develop ways by which dyskinesias may be treated.

The present invention relates to the treatment of dyskinesias using a compound with the general formula (I)



(I)

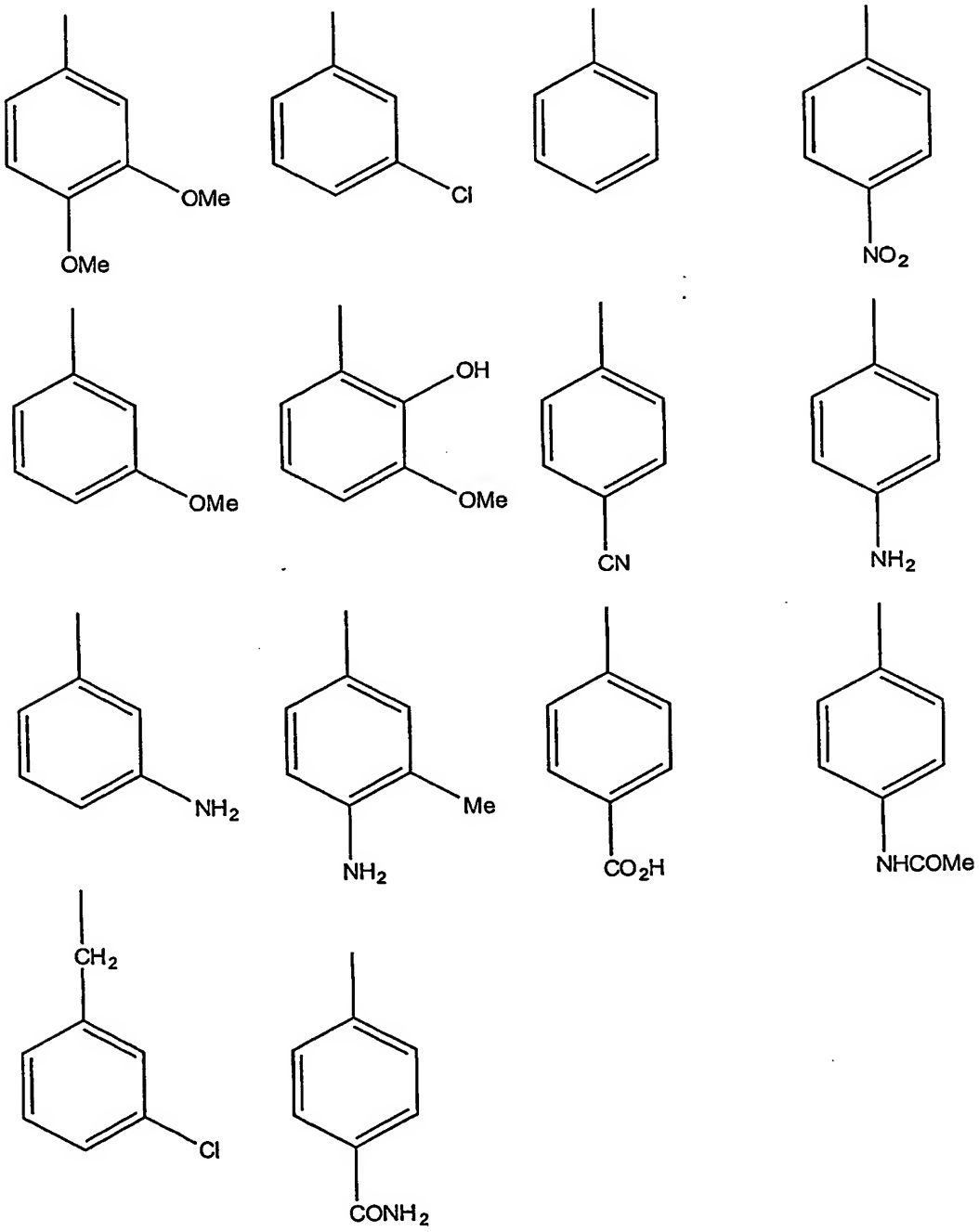
wherein R is an aryl group, such as phenyl or benzyl, which is optionally substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, halogen, hydroxyl, amino, nitro, amido, nitrile or a carboxyl group;

R^1 is C_{1-6} alkyl or hydrogen;

R^2 is C_{1-6} alkoxy, hydrogen, hydroxyl, or halogen; and

R^3 is C_{1-6} alkoxy, hydrogen, hydroxyl, or halogen,

Preferably R is selected from one of the following groups:

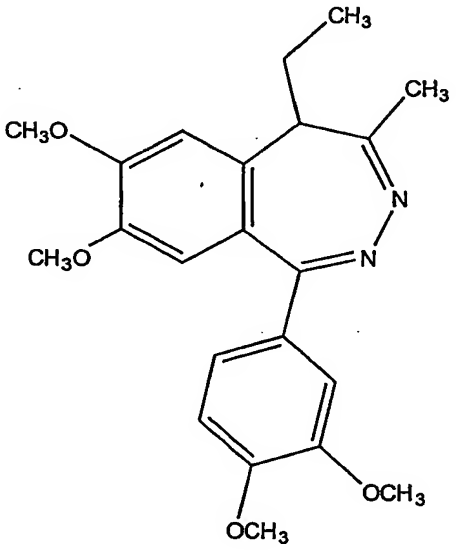


When R^1 is an alkyl group, it is preferred that R^1 is C_{1-3} alkyl with C_2 alkyl (ethyl) being most preferred.

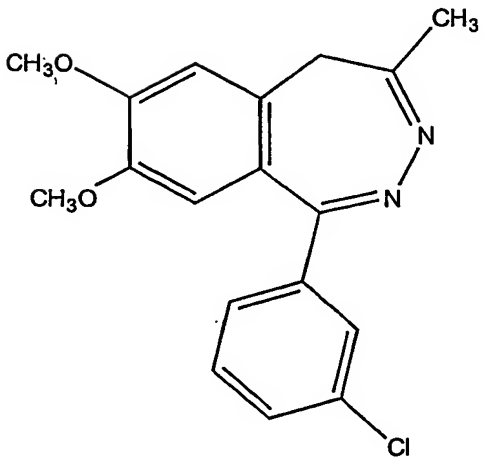
When R^2 is an alkoxy group, it is preferred that R^2 is C_{1-3} alkoxy with C_1 alkoxy (methoxy) being most preferred.

When R^3 is an alkoxy group, it is preferred that R^3 is C_{1-3} alkoxy with C_1 alkoxy (methoxy) being most preferred.

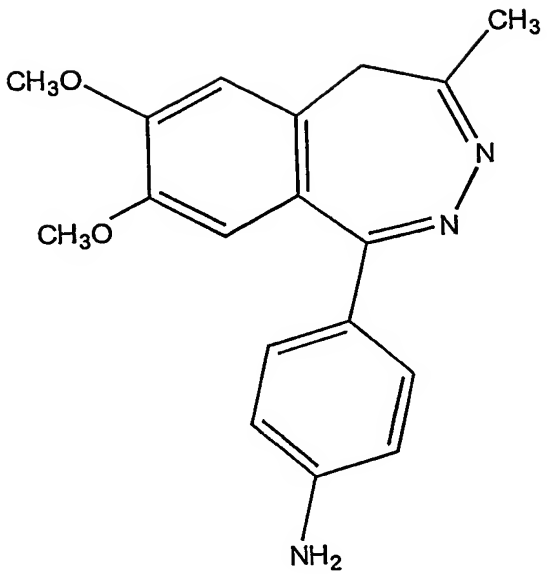
It is preferred that the compound of formula (I) is selected from the group of Tofisopam, Girisopam and Nerisopam, which are as follows:



Tofisopam



Girisopam



Nerisopam

Most preferably the compound of formula (I) is Tofisopam.

According to a first aspect of the present invention, there is provided a use of a compound of general formula (I) for the manufacture of a medicament for the treatment of dyskinesia.

According to a second aspect of the present invention, there is provided a composition for use in the treatment of dyskinesia comprising a therapeutically effective amount of a compound of general formula (I) and a pharmaceutically acceptable vehicle.

According to a third aspect of the present invention, there is provided a method for the treatment of dyskinesia comprising administering to a person or animal in need of said treatment a therapeutically effective amount of a compound of general formula (I).

According to a fourth aspect of the present invention, there is provided a use of an agent which modulates the activity of receptors with ligands of general formula (I) for the manufacture of a medicament for the treatment of dyskinesia.

By "receptors" we mean receptors located on the terminals of the striatal output neurons that project to the internal and external segments of the globus pallidus and the pars reticulata of the substantia nigra in the brain and thereby induce a neuronal signal which reduces dyskinesia and for which molecules of general formula (I) act as ligands.

Several classes of agent may be used according to the fourth aspect of the invention. These include:

(i) exogenous 2, 3 benzodiazepine receptor ligands;

(ii) compounds which enhance synthesis of endogenous 2,3 benzodiazepine receptor ligands;

(iii) compounds which enhance release of endogenous 2,3 benzodiazepine receptor ligands;

(v) compounds which block the rate of inactivation or metabolism of endogenous 2,3 benzodiazepine receptor agonists; and

(vi) compounds which promote/increase 2,3 benzodiazepine receptor expression and/or transcription.

The invention is based upon our studies relating to the neural mechanisms underlying movement disorders. Although we do not wish to be bound by any hypothesis, we believe that movement disorders involve abnormal activity of basal ganglia output pathways and in many cases this is brought about by abnormal function of striatal efferent pathways. These consist of a "direct" pathway to the medial or internal segment of the globus pallidus and the pars reticulata of the substantia nigra and a "indirect" pathway to the lateral or external segment of the globus pallidus. One of the pathophysiological hallmarks of dyskinesia is overactivity of the direct striatal output pathway. Conversely, in Parkinson's disease the direct striatal output pathway is

underactive and the indirect striatal output pathway is overactive. We believe compounds of general formula (I) bind to receptors located on the terminals of the striatal output neurons that project to the internal and external segments of the globus pallidus and the pars reticulata of the substantia nigra and thereby induce a neuronal signal which reduces dyskinesia.

WO 99/06408 and WO 01/04122 disclose molecules which have a core 2, 3 benzodiazepine tricyclic structure with some similarity to the compounds of general formula (I). The prior art speculates that such compounds may be used in the treatment of a variety of medical conditions (e.g. Parkinson's disease). However, the compounds used according to the invention are distinguished over this prior art in that the rings have different substituents (in particular at R, R^2 and R^3). Furthermore, the compounds used according to the invention have surprising utility for treating dyskinesias, that is to say excessive involuntary movements, and not Parkinson's disease *per se*, which is characterised by a poverty of movement.

The present inventors conducted experiments with the molecule Tofisopam which led them to realise that compounds of general formula (I) are highly effective for the treatment of dyskinesias. For instance, it was found that dyskinesias (e.g. chorea and dystonia) do not develop, or are at least reduced, when the compounds are given to subjects on dopamine-replacement therapy for the treatment of a movement disorder.

The compounds (and compositions or medicaments containing them) may be used to treat many types of dyskinesia. For instance the compounds may be used to treat dyskinesia associated with Huntington's disease, idiopathic torsion dystonia, tardive dyskinesia or off-dystonia in Parkinson's disease and most particularly for dyskinesia associated with movement disorders such as parkinsonism (e.g. idiopathic Parkinson's disease, post-encephalitic parkinsonism or parkinsonism resulting from head injury), treatment of schizophrenia, drug intoxication, manganese poisoning and the like.

The compounds may also be used in the treatment of dyskinesias which manifest as hyperkinetic activity (e.g. Tourette's syndrome attention deficit hyperactivity (ADHD)).

The compounds are also useful for treatment of dyskinesias which arise as a side-effect of other therapeutic agents. For instance, the compounds are useful for the treatment of dyskinesia associated with ropinirole, pramipexole, cabergoline, bromcriptine, lisuride, pergolide, L-DOPA or apomorphine treatment. The compounds are preferably used for the treatment of dyskinesia associated with L-DOPA or apomorphine treatment.

The compounds are particularly useful for treating dyskinesia caused by agents used to treat movement disorders such as parkinsonism. In this respect a preferred use of the compounds is in the treatment of dyskinetic side-effects associated with L-DOPA or apomorphine therapy for parkinsonism.

The compounds may be used to treat existing dyskinesias but may also be used when prophylactic treatment is considered medically necessary. For instance, when it is considered necessary to initiate L-DOPA therapy and it is feared that dyskinesias may develop.

The compounds may be used to treat dyskinesia as a monotherapy (i.e. use of the compound alone) or they may be used as an adjunct to other therapeutic agents. For instance, the compounds may be co-administered with therapeutic agents to prevent dyskinetic side-effects caused by such therapeutic agents (e.g. as an adjunct to L-DOPA or apomorphine given to treat parkinsonian patients).

In preferred embodiments of the invention the compound of general formula (I) or agents according to the fourth aspect of the invention may be combined with therapeutic agents such as:

(a) therapeutic agents used in the treatment of parkinsonism, including Parkinson's disease (e.g. L-DOPA, Chloro-APB, apomorphine, ropinirole, pramipexole, cabergoline, bromcriptine, lisuride or pergolide)

(b) other therapeutic agents used in the treatment of dyskinesia (e.g. non selective, δ or μ-opioid receptor antagonists, α_2-adrenoreceptor-antagonists, cannabinoid CB_1-antagonists, Histamine H3 agonists, mGLuR antagonists NMDA receptor-antagonists, Gpi lesion/deep brain stimulation).

(c) therapeutic agents used as neuroleptics for the treatment of schizophrenia, psychosis and the like (e.g. agents with dopamine receptor antagonist properties, haloperidol clozapine, fluphenazine and sulpiride.

Compositions according to the first, second, third or fourth aspects of the invention may take a number of different forms depending, in particular on the manner in which the composition is to be used. Thus, for example, the composition may be in the form of a powder, tablet, capsule, liquid, ointment, cream, gel, hydrogel, aerosol, spray, micelle, transdermal patch liposome or any other suitable form that may be administered to a person or animal. It will be appreciated that the vehicle of the composition of the invention should be one which is well tolerated by the subject to whom it is given and enables delivery of the compounds to the brain.

The composition of the invention may be used in a number of ways. For instance, systemic administration may be required in which case the compound may be contained within a composition which may, for example, be ingested orally in the form of a tablet, capsule or liquid. Alternatively, the composition may be administered by injection into the blood stream. Injections may be intravenous (bolus or infusion) or subcutaneous (bolus or infusion). The compounds may also be administered by inhalation (e.g. intranasally).

Compounds as defined by general formula (I) may also be administered centrally by means of intracerebral, intracerebroventricular, or intrathecal delivery.

The compositions are particularly useful when incorporated into patches that may be applied to the skin for transdermal delivery of the compounds according to general formula (I).

The compound may also be incorporated within a slow or delayed release device. Such devices may, for example, be inserted on or under the skin and the compound may be released over weeks or even months. Such a device may be particularly useful for patients with long term dyskinesia such as patients on continuous L-DOPA therapy for the treatment of Parkinsonism. The devices may be particularly advantageous when a compound is used which would normally require frequent administration (e.g. at least daily ingestion of a tablet or daily injection).

It will be appreciated that the amount of a compound required is determined by biological activity and bioavailability which in turn depends on the mode of administration, the physicochemical properties of the compound employed and whether the compound is being used as a monotherapy or in a combined therapy. The frequency of administration will also be influenced by the abovementioned factors and particularly the half-life of the compound within the subject being treated.

Known procedures, such as those conventionally employed by the pharmaceutical industry (e.g. *in vivo* experimentation, clinical trials etc), may be used to establish specific formulations of compositions and precise therapeutic regimes (such as daily doses of the compounds and the frequency of administration).

Generally, a daily dose of between 0.01μg/kg of body weight and 1.0g/kg of body weight of a compound of general formula (I) may be used for the treatment of dyskinesia depending upon which specific compound is used, more preferably, the daily dose is between 0.01mg/kg of body weight and 100mg/kg of body weight.

Purely by way of example a suitable dose of tofisopam for treating L-DOPA induced dyskinesia in subjects with Parkinson's disease is between 0.1mg/kg/day and 100mg/kg/day (depending upon the health status of the individual). It is preferred that between 0.25mg/kg/day and 20mg/kg/day of tofisopam is given to a person daily and is most preferred that about 10mg/kg/day tofisopam is given for treating dyskinesia induced by L-DOPA.

It will be appreciated that the required dose will be effected by the route of administration. When tofisopam is given intravenously 0.1-10 mg/kg is a preferred dose whereas higher doses (e.g 5 -15 mg/kg) may be a suitable dose orally.

By way of further example suitable doses of Girisopam or Nerisopam are preferably 0.5-30 mg/kg.

Daily doses may be given as a single administration (e.g. a daily tablet for oral consumption or as a single daily injection). Alternatively the compound used may require administration twice or more times during a day. As an example, tofisopam for treating L-DOPA induced dyskinesia in patients with Parkinson's disease may be administered as two (or more depending upon the severity of the dyskinesia) daily doses of between 25mg and 5000mg in tablet form. A patient receiving treatment may take a first dose upon waking and then a second dose in the evening (if on a two dose regime) or at 3 or 4 hourly intervals thereafter. Alternatively a slow release device may be used to provide optimal doses to a patient without the need to administer repeated doses.

An embodiment of the present invention will now be described, by way of example, with reference to the accompanying drawings, in which;

Figure 1 is a graph illustrating the effect of Tofisopam on motor activity induced by L-DOPA in parkinsonian (MPTP-lesioned) marmosets in Example 1;

Figure 2 is a bar chart illustrating the dose/response relationship of the effect of Tofisopam on motor activity induced by L-DOPA, cumulated over a 4hour observation period, in parkinsonian (MPTP-lesioned) marmosets of Example 1; and

Figure 3 is a series of bar charts (A – D) illustrating the dose/response relationship of the effect of Tofisopam on activity induced by L-DOPA, broken down into 1hour time bins, in parkinsonian (MPTP-lesioned) marmosets of Example 1.

For all figures: * indicates $P < 0.05$; ** indicates $P < 0.01$; and*** indicates $P < 0.001$ compared to L-DOPA + vehicle; non-parametric one-way repeated measures ANOVA (Friedman test) followed by Dunn's multiple comparison test.

EXAMPLE 1

The effect of Tofisopam on L-DOPA-induced dyskinesia was assessed in the MPTP-lesioned marmoset model of Parkinson's disease.

1.1. Methods

1.1.1 Preparation of MPTP-lesioned marmoset model of Parkinson's disease

Marmosets (Callithrix jacchus) (bred in a closed colony at the University of Manchester) are rendered parkinsonian by subcutaneous injection of 2mg kg^{-1} MPTP for 5 consecutive days. The marmosets are allowed to recover for a minimum of 10 weeks until their parkinsonism becomes stable. The degree of activity and disability before and after MPTP treatment is assessed using a combination of scales as described in section 1.1.2. Animals are then treated with L-DOPA for at least 3 weeks to prime them to elicit dyskinesia.

1.1.2 Assessment of behaviour

Behaviour was assessed using the following scales:

(a) **Activity** – a measure of the motor activity of the animals that is assessed by passive infra-red sensors every five minutes. This measure assesses all movements of the animal including dyskinesia.

(b) **Parkinsonian disability** – non-parametric measures based on the following scales:

Mobility score: 0 = no movement, 1 = movement of head on the floor of the cage, 2 = movement of limbs, but no locomotion, on the floor of the cage, 3 = movement of head or trunk on wall of cage or perch, 4 = movement of limbs, but no locomotion, on wall of cage or perch, 5 = walking around floor of cage or eating from hopper on floor, 6 = hopping on floor of cage, 7 = climbing onto wall of cage or perch, 8 = climbing up and down the walls of the cage or along perch, 9 = running, jumping, climbing between cage walls / perch / roof, uses limbs through a wide range of motion and activity.

(a) **Dyskinesia** – non-parametric measures based on the following scale:

Dyskinesia score: 0 = Absent, 1 = Mild, fleeting, 2 = Moderate, not interfering with normal activity, 3 = Marked, at times interfering with normal activity, 4 = Severe, continuous, replacing normal activity.

The behavioural tests were assessed every 30 minutes for 4 hours, by post hoc analysis of video-recordings by an observer blinded to the treatment.

1.1.3 Treatments

Marmosets received all treatments as described in Table 1. The treatments were randomised such that on each day all marmosets received one of the treatments. There was at least 48 hours washout between treatments.

Table 1

Treatment Number	Treatment	Route of administration
1	vehicle	oral
2	L-DOPA (15-17.5mg/kg)	oral
3	L-DOPA (15-17.5mg/kg) + Tofisopam (5mg/kg)	oral
4	L-DOPA (15-17.5mg/kg) + Tofisopam (10mg/kg)	oral
5	L-DOPA (15-17.5mg/kg) + Tofisopam (15mg/kg)	oral
6	L-DOPA (15-17.5mg/kg) + Tofisopam (20mg/kg)	oral

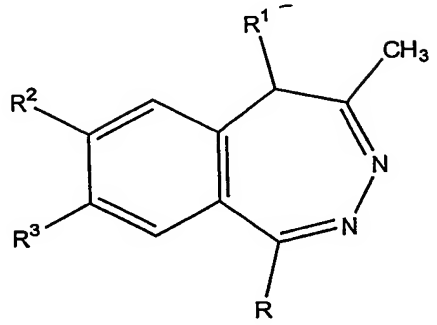
1.2. Results

Figures 1, 2 and 3 illustrate the effect of Tofisopam treatment on L-DOPA-induced motor counts in the MPTP-lesioned marmoset model of Parkinson's disease. These data demonstrate that compound as defined by general formula (I) cause a dose-dependent reduction in the severity of L-DOPA-induced dyskinesia.

The MPTP-lesioned primate is the 'gold standard' preclinical model of Parkinson's disease. Therefore, these data are highly predictive of a beneficial therapeutic effect of the compounds in the treatment of L-DOPA-induced dyskinesia in Parkinson's disease patients and other dyskinesias.

CLAIMS

1. The use of a compound of general formula (I)



(I)

wherein R is an aryl group selected from phenyl or benzyl, which is optionally substituted with a C_{1-6} alkyl, C_{1-6} alkoxy, halogen, hydroxyl, amino, nitro, amido, nitrile or a carboxyl group;

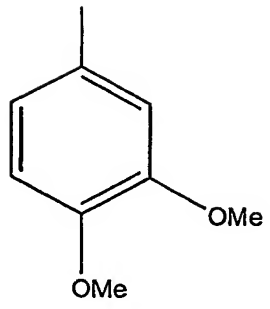
R^1 is C_{1-6} alkyl or hydrogen;

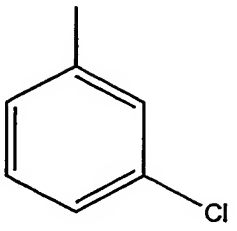
R^2 is C_{1-6} alkoxy, hydrogen, hydroxyl, or halogen; and

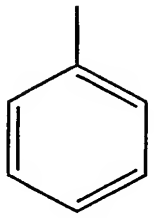
R^3 is C_{1-6} alkoxy, hydrogen, hydroxyl, or halogen,

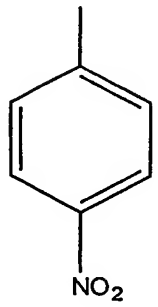
for the manufacture of a medicament for the treatment of dyskinesia.

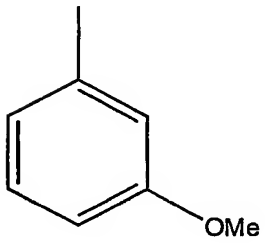
2. The use according to claim 1, wherein R is selected from the following groups:

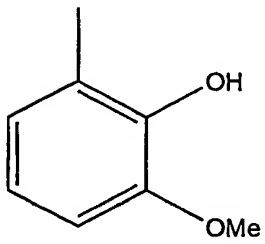


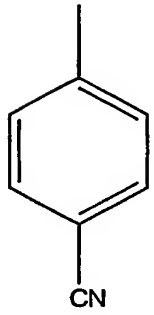


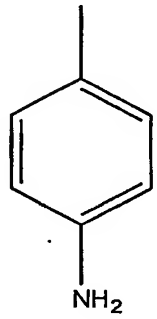


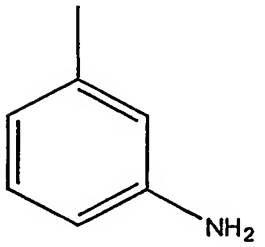


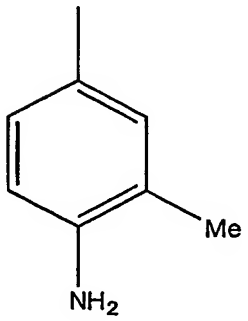


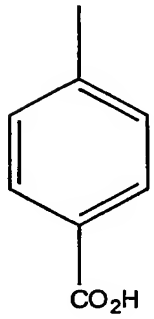


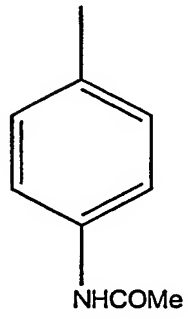


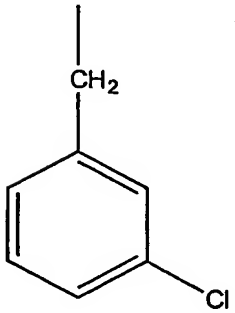


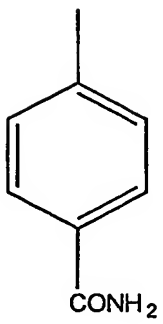










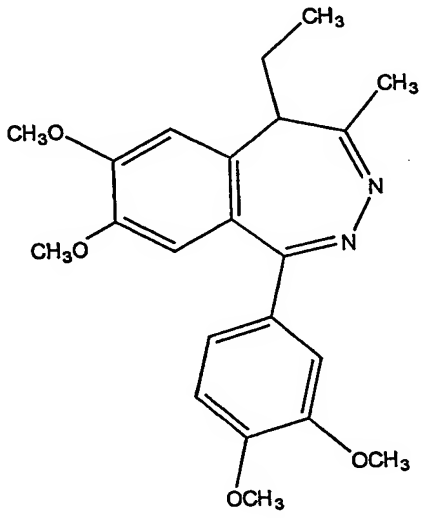


3. The use according to claim 1 or 2, wherein when R^1 is an alkyl group it is C_2 alkyl (ethyl).

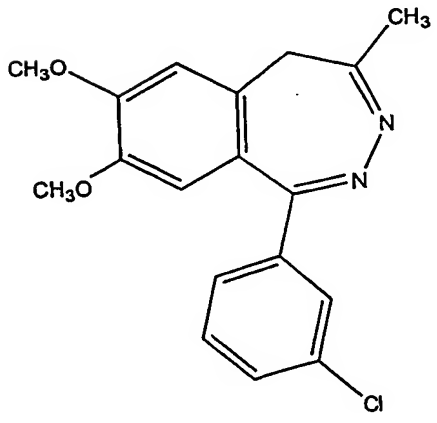
4. The use according to claim 1, 2 or 3, wherein when R^2 is an alkoxy group, it is C_1 alkoxy (methoxy).

5. The use according to any one of the preceding claims, wherein when R^3 is an alkoxy group, it is C_1 alkoxy (methoxy).

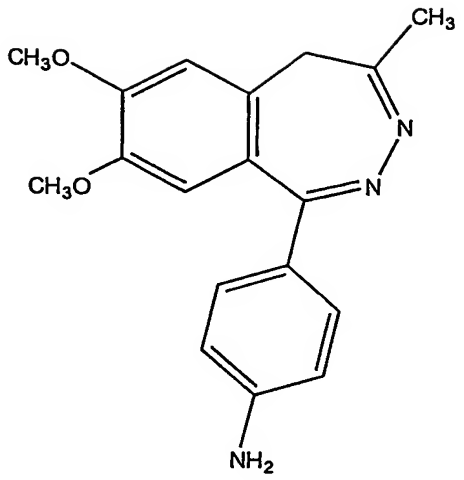
6. The use according to any one of the preceding claims, wherein the compound of formula I is selected from the group comprising Tofisopam, Girisopam and Nerisopam (shown below):



Tofisopam



Girisopam



Nerisopam

7. The use according to claim 6, wherein the compound of formula I is Tofisopam.

8. The use according to any preceding claim, for the treatment of dyskinesia associated with movement disorders.

9. The use according to claim 8, for the treatment of dyskinesia associated with parkinsonism.

10. The use according to claim 9 wherein the parkinsonism is idiopathic Parkinson's disease or post-encephalitic parkinsonism.

11. The use according to claim 9 wherein the parkinsonism results from head injury, the treatment of schizophrenia, drug intoxication or manganese poisoning.

12. The use according to any one of claims 1 - 7 for the treatment of dyskinesia associated with Huntington's disease, idiopathic torsion dystonia, or off-dystonia in Parkinson's disease.

13. The use according to anyone of claims 1-7 for the treatment of hyperkinetic disorder associated with Tourette's syndrome and ADHD.

14. The use according to any one of claims 1 - 7 for the treatment of dyskinesia which arises as a side-effect of a therapeutic agent.

15. The use according to claim 14 for the treatment of dyskinesia associated with agents used to treat movement disorders.

16. The use according to claim 14 or 15 wherein the agent is used to treat parkinsonism.

17. The use according to claim 16 wherein the agent is a dopamine precursor.

18. The use according to claim 16 wherein the agent is a dopamine receptor agonist.

19. The use according to claim 16 wherein the agent in L-DOPA.

20. The use according to claim 16 wherein the agent is one of Chloro-APB, apomorphine, ropinirole, pramipexole, cabergoline, bromcriptine, lisuride or pergolide.

21. The use according to claim 14 wherein the agent is used to treat schizophrenia or other psychosis.

22. The use according to claim 21 wherein the agent is a neuroleptic.

23. The use according to claim 21 wherein the agent has dopamine receptor antagonist properties.

24. The use according to claim 21 wherein the agent is haloperidol clozapine, fluphenazine or sulpiride.

25. The use according to any preceding claim for prophylactic treatment.

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FIGURE 1

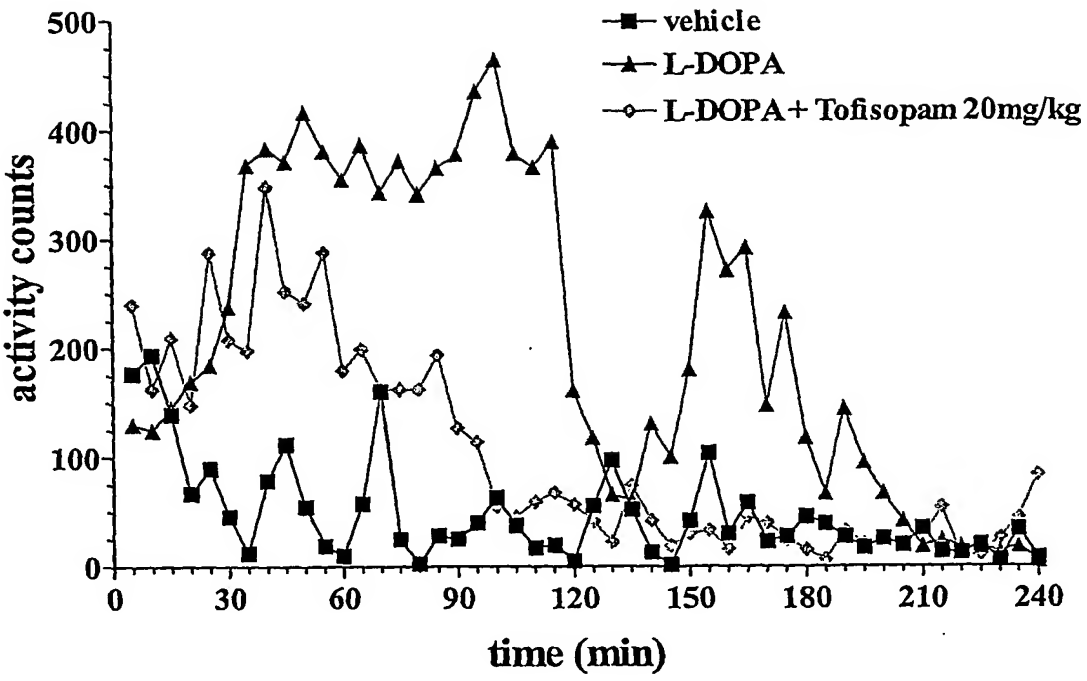

vehicle
L-DOPA
L-DOPA+ Tofisopam 20mg/kg
activity counts
500
400
300
200
100
0
0
30
60
90
120
150
180
210
240
time (min)

FIGURE 2

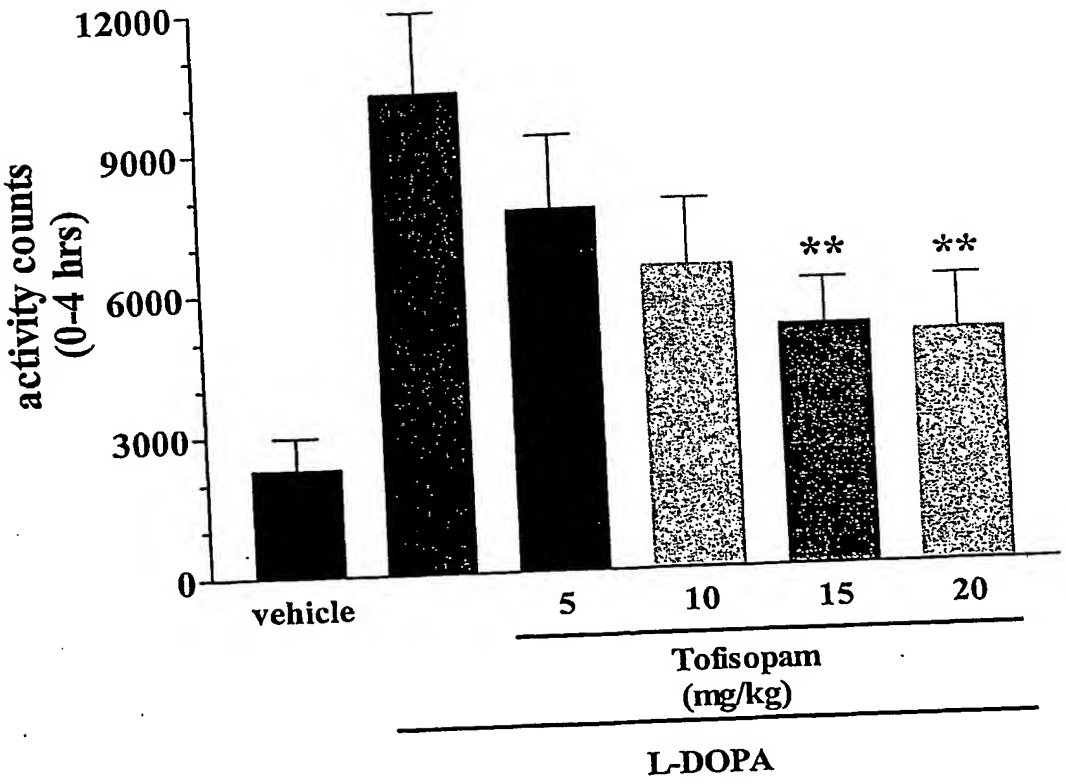

12000
9000
6000
3000
0
activity counts
(0-4 hrs)
**
**
vehicle
5
10
15
20
Tofisopam
(mg/kg)
L-DOPA

FIGURE 3A

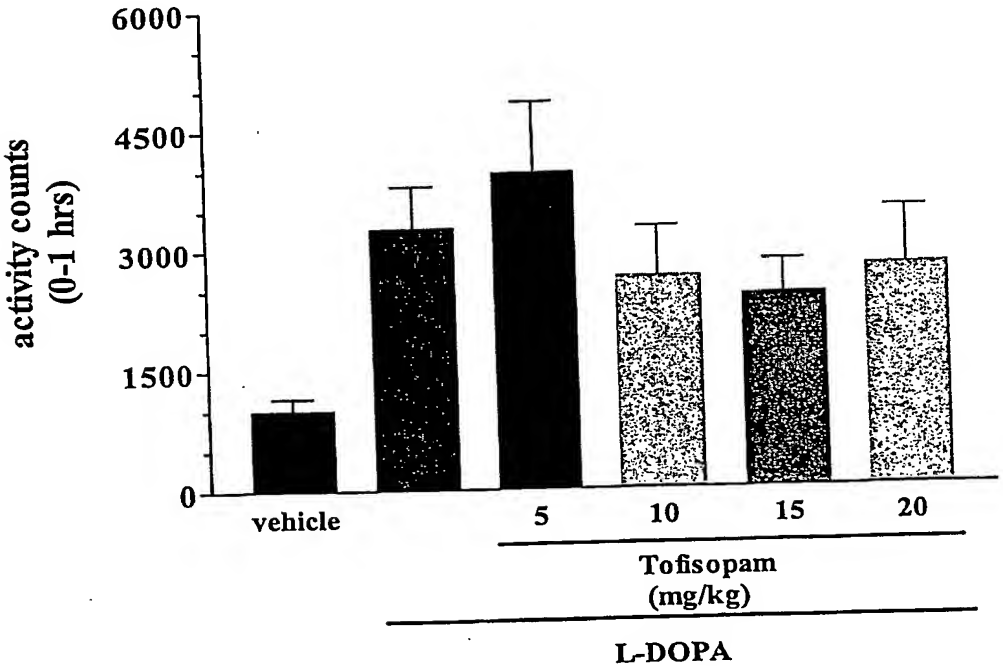

6000
4500
3000
1500
0
activity counts
(0-1 hrs)
vehicle
5
10
15
20
Tofisopam
(mg/kg)
L-DOPA

FIGURE 3B

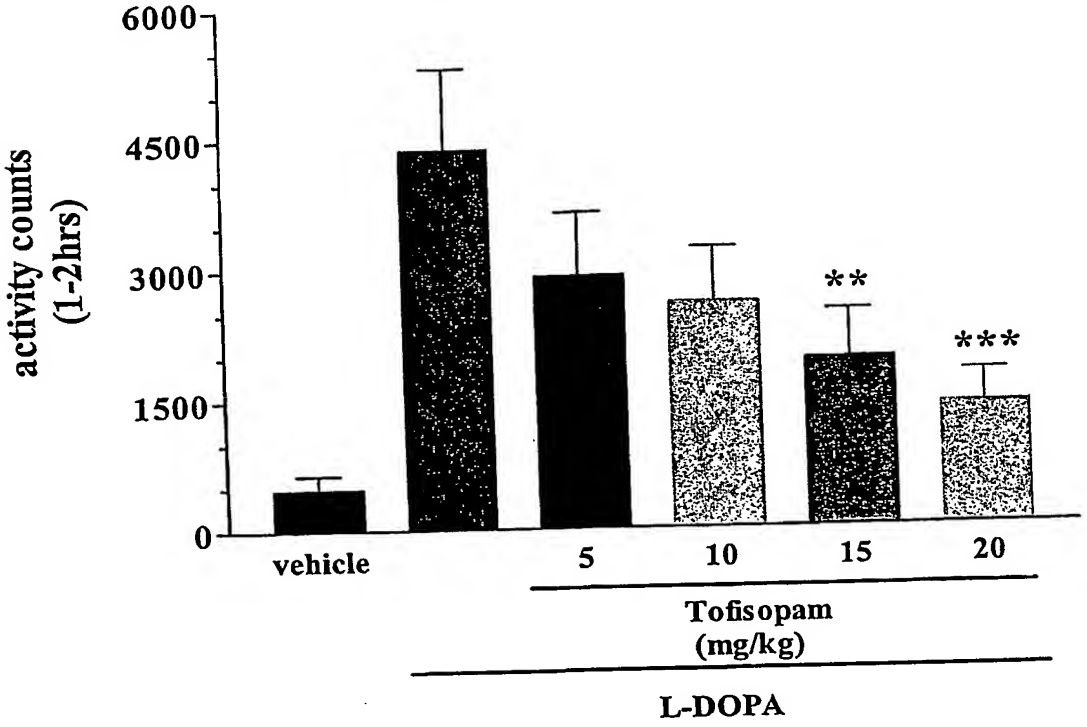

6000
4500
3000
1500
0
activity counts
(1-2hrs)
**
***
vehicle
5
10
15
20
Tofisopam
(mg/kg)
L-DOPA

FIGURE 3C

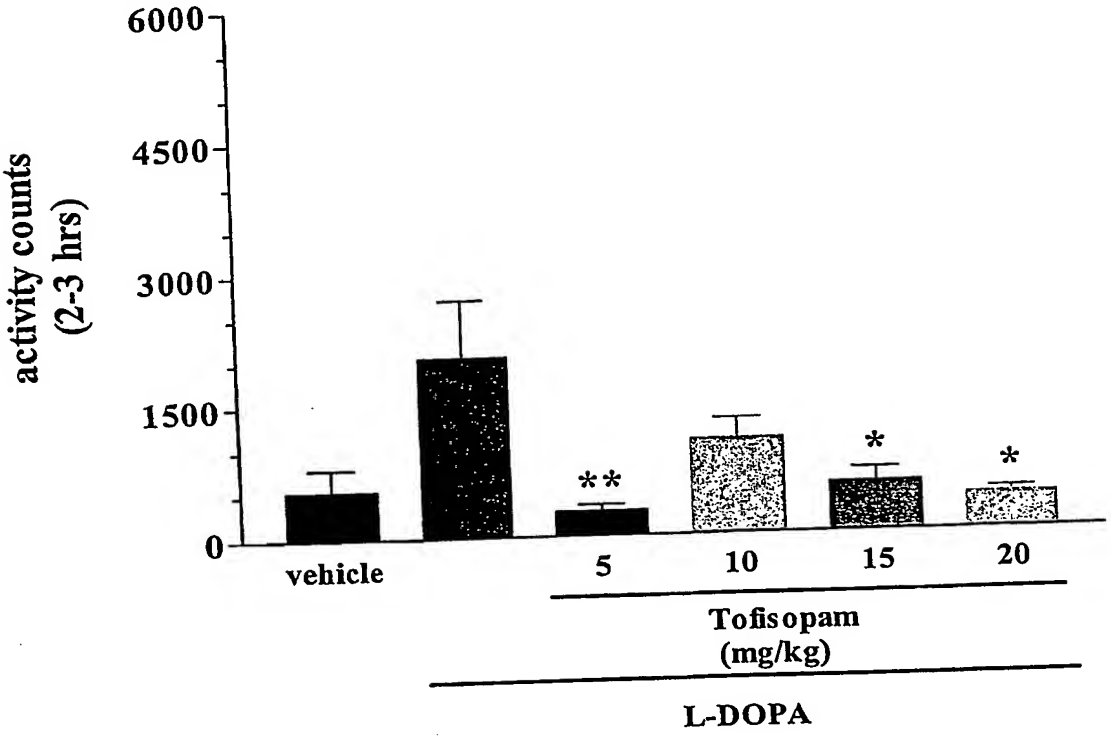
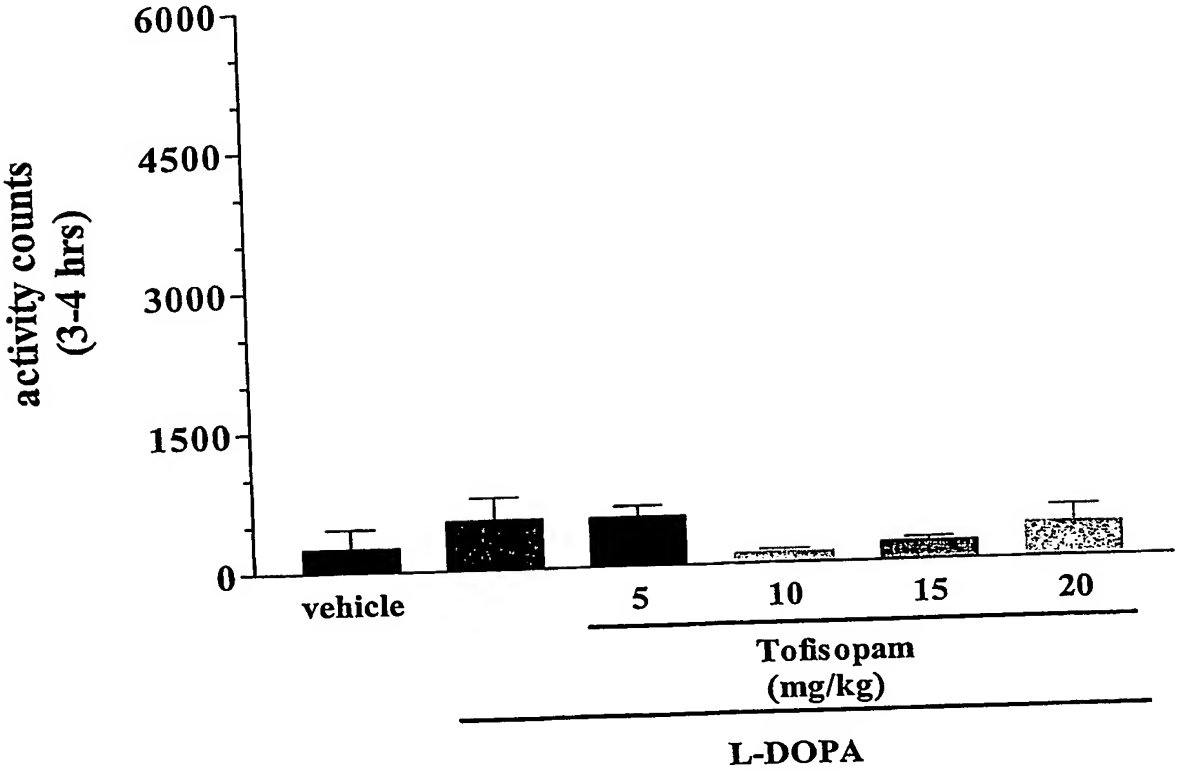

6000
4500
3000
1500
0
activity counts
(2-3 hrs)
**
*
*
vehicle
5
10
15
20
Tofisopam
(mg/kg)
L-DOPA

FIGURE 3D


6000
4500
3000
1500
0
activity counts
(3-4 hrs)
vehicle
5
10
15
20
Tofisopam
(mg/kg)
L-DOPA